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| 10/553,120 | 10/14/2005 | Tatsuo Kimura | 279431US0PCT | 1699 |

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| EXAMINER | |
|---|---|
| HUANG, GIGI GEORGIANA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

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| 10/24/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/553,120 | KIMURA ET AL. | |
| | Examiner | Art Unit | |
| | GIGI HUANG | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/2005, 7/19/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of Group I and the specific compound of 1 -[3-(2-(1 -benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol ($R^1$ and $R^2$ are hydrogen atoms, $R^3$ is OH, m is 2, n is 3, and p is 1) in the reply filed on August 12, 2008 is acknowledged. The traversal is on the grounds that there is no burden, the Examiner did not show lack of unity of a lack of common structural element or a lack of the same activity. This is not found persuasive because the instant case is submitted under 35 U.S.C. 371, the Unity of Invention practice in MPEP §1850 and MPEP §1893.03(d) was followed, not restriction practice. Thus the criteria for burden stated in MPEP §803 for national applications filed under 35 U.S.C. 111(a) does not apply (MPEP §801). The lack of unity has been addressed in the previous action as it clearly addresses that there are separate cores (see Page 5 and 6) with respect to the cores formed from choice B compared to choice C yielding two different cores. As for the number of claimed compounds, it is unlikely that all or practically all of the compounds have the same effect purely based on steric hindrance for all the compounds with different cores and configurations to affect the same receptor (see Danziger et al.). In addition, many conditions and diseases in the claims have very distinct approaches for treatment since specific pathways must be utilized dependent on the condition. The compounds used for the pathway for Ischemic optic neuropathy are likely to be distinctly different than retinopathy. As a result, the compounds will not all share a common effect.

As the technical feature did not contribute over the art, the restriction was applied appropriately.

The requirement is still deemed proper and is therefore made FINAL.

***Status of Application***

2. Applicant's election with traverse of Group I and the specific compound of 1 -[3-(2-(1 -benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol ($R^1$ and $R^2$ are hydrogen atoms, $R^3$ is OH, m is 2, n is 3, and p is 1) for the examination.

3. Claims 1-7 are present for examination at this time.

***Information Disclosure Statement***

4. The information disclosure statement filed 10/14/2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because there is no translation of Hyojun Ganka Gaku. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the drawn to a preventive and/or remedy for retinal nerve diseases comprising an alkyl derivative represented by the claimed formula. There is inadequate written description for what conditions are retinal nerve diseases. The term "retinal nerve diseases" is not defined and it does not address which conditions are encompassed, which structures are affected, the etiology, nor the extent of the condition. The optic nerve is in the center of the retina, there are peripheral nerves, rods, cones, whereby it is inadequately describe as to what conditions are in possession of Applicant other than glaucoma, diabetic retinopathy, retinal artery obstruction, retinal venous obstruction, macular degeneration, and retinopathy of prematurity which is disclosed in the specification (Page 1 line 17-22, Page 2 line 15-22).

The term "retinal nerve diseases" is not adequately described as it does not describe adequately which structures are affected, degree of involvement, the etiology, the extent of the condition to ascertain what conditions would fulfill the description. As a

result, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

Thereby, while having written description glaucoma, diabetic retinopathy, retinal artery obstruction, retinal venous obstruction, macular degeneration, and retinopathy of prematurity, the specification does not provide sufficient descriptive support for the myriad of conditions embraced by the claims, and only glaucoma, diabetic retinopathy, retinal artery obstruction, retinal venous obstruction, macular degeneration, and retinopathy of prematurity are to be considered.

7. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment, does not reasonably provide enablement for prevention or complete remedy for retinal nerve diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The accepted definition of "remedy" in Stedman's Medical Dictionary is "an agent that cures disease or alleviates its symptoms" (see Stedman's sheets). Applicant has reasonably demonstrated/disclosed that the claimed compound is useful as a therapeutic agent for treating/alleviating conditions as a result of retinal ischemia of the optic nerve within the described conditions of glaucoma, diabetic retinopathy, retinal artery obstruction, retinal venous obstruction, and retinopathy of prematurity which is disclosed in the specification; but not macular degeneration which although described, its etiology is unknown and thereby not directed to retinal ischemia.

However, the breath of the claims is so broad as to encompass using the claimed compound to prevent and cure every ocular condition related to the optic nerve, retinal peripheral nerves, rods, or cones, which is clearly beyond the scope of the instantly disclosed/claimed invention. Please note that the term "prevent" is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic", "treat", or "alleviate", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes) – including preventing such disorders as Leber's Hereditary Optic Neuropathy or Age-related Macular Degeneration, which is clearly not recognized in the medical art as being a totally preventable or curable condition.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

*(1) The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to the prevention of an ocular condition by administering the claimed compound (elected compound is 1-[3-(2-(1-benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol or T-817-MA). Thus, the claims taken together with the specification imply that all ocular conditions related to the optic nerve, retinal peripheral nerves, rods, or cones are preventable and curable with the administration of the claimed compound (elected compound is 1-[3-(2-(1-benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol or T-817-MA).

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

Newman (hereditary Optic Neuropathies…) addresses Leber's hereditary optic neuropathy (LHON) is a mitochondrially-inherited condition where the optic nerve undergoes neuropathy related to changes in the mitochondrial DNA. Presentation is typically men in their twenties and thirties but symptoms can happen at any age to both men and women. The mitochondria are unable to provide adequate energy to the cells and the optic nerve and retina become damaged or necrosis. There is no current conventional treatment, cure, or method of prevention.

Schmidt-Erfurth ( Management of neovascular age-related macular degeneration) addresses Age-related Macular Degeneration and how only recently gaining new insights in the pathogenesis of the disease are allowing for improved treatment for the *management* of the disease, not *prevention or a cure* as the etiology is still not clear for those skilled in the art.

The Merck Manual supports that there is no known etiology for age-related macular degeneration.

(5) The relative skill of those in the art:

The relative skill is high.

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for the delivery of elected compound of 1-[3-(2-(1-benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol maleate (or T-817-MA) in the single working example for retinal ischemia to the optic nerve. There is reasonable expectation that the described conditions: glaucoma, diabetic retinopathy (see Merck sheet), retinal artery obstruction, retinal venous obstruction, and retinopathy of prematurity which are caused by and related to retinal nerve ischemia are treatable/alleviated.

However, the specification does not provide for the prevention or the cure of every ocular condition related to the optic nerve, retinal peripheral nerves, rods, or cones, including macular degeneration.

*(8) The quantity of experimentation necessary*:

Considering the state of the art as discussed by the references above, particularly with regards to prevention of all ocular conditions and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the

specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a preventive and/or remedy for retinal nerve diseases comprising an alkyl derivative represented by the formula but there is no specific method step of administration recited nor a specific "method" recitation. It is unclear if it is a method of administration for the compound for the treatment/alleviation of a condition or if a compound claim with recitation of intended use. For purposes of prosecution, the claims are viewed as methods of prevention and/or remedy of retinal nerve disease comprising the administration of the compound.

***Claim Rejections - 35 USC § 102***

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Saitoh et al. (WO 03/035641).

It is noted that U.S. Pat. No. 7087594 will be used as the translation. All references are to the U.S. Pat.

Saitoh et al. teaches an alkyl ethers including 1 -[3-(2-(1 -benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol and its salts (e.g. hydrochloride and acetamide-Examples 9-11) for the use of accelerating neurite outgrowth, nerve regeneration, and protection of neurons, as a therapeutic agent for disease in central and peripheral nerves which includes the optic nerve (as evidenced by Moalen et al. whereby the optic nerve represents the CNS-see Abstract).

All the critical elements are taught by the cited reference and thus the claims are anticipated (Abstract, Col. 6 line 14-68, Col. 21 line 19-Col. 22 line 45, Col. 27 Example 9-Col. 30 line 68, Col. 107 line 30-40).

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claim 1-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Saitoh et al. (U.S. Pat. No. 7087594).

Saitoh et al. teaches an alkyl ethers including 1 -[3-(2-(1 -benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol and its salts (e.g. hydrochloride and acetamide-Examples 9-11) for the use of accelerating neurite outgrowth, nerve regeneration, and protection of neurons, as a therapeutic agent for disease in central and peripheral nerves which

includes the optic nerve (as evidenced by Moalen et al. whereby the optic nerve represents the CNS-see Abstract).

All the critical elements are taught by the cited reference and thus the claims are anticipated (Abstract, Col. 6 line 14-68, Col. 21 line 19-Col. 22 line 45, Col. 27 Example 9-Col. 30 line 68, Col. 107 line 30-40).

The applied reference has a common assignee and inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

***Conclusion***

14. Claims 1-7 are rejected.

15. The following piece of art is noted: Nakada et al. U.S. Pat. No. 7342043.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612